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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/460,292	12/10/99	MANGELSDORF	D UTSD:596

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EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/460,292	Applicant(s) MANGELSDORF ET AL.	
	Examin r Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sh et with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10-19-00* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *15-20,30-43 and 46-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,21-29,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

This application is an original application filed December 10, 1999, which claims benefit to provisional application 60/111,894, filed December 10, 1998.

Applicants response to the Restriction requirement has been received, October 19, 2000, paper number 9. Election of Group I, claims 1-14, 21-29, 44 and 45 has been elected without traverse. Claims 15-20, 30-43 and 46-58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-58 are pending. Claims 1-14, 21-29, 44 and 45 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11,21-29, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a disruption of the endogenous nuclear oxysterol receptor gene (LXRα), wherein said disruption in said mouse results in the decrease of the LXRα protein and said mouse exhibits the inability to

respond normally to dietary cholesterol does not reasonably provide enablement for any non-human transgenic mammal whose cells contain at least one non-functional allele. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Claims 1-9 and 14 encompass a non-human transgenic mammal and claims 44 and 45 encompass a cell comprising at least one non-functional endogenous LXRα allele. Claims 10-13 encompass a disruption or substitution of the regulatory region of the LXRα allele with an inducible/repressible promoter. Claims 21-29 encompass methods of screening a candidate substance for the ability to reduce cholesterol (claims 21-26) and the ability to increase bile acid synthesis (claims 27-29) with said transgenic animal. The claims encompass generation of any transgenic non-human animal. Since no phenotype resulting from the disruption is recited nor is the definition of non-functional allele clearly defined in the specification, any non-human animal having any disruption would fulfill the limitation of the claim with respect to function of the encoded receptor polypeptide. The specification teaches specifically how to create a transgenic mouse recited in the basis of the rejection, *supra*. However, the specification is silent with respect to guidance or example for the creation of <u>any</u> transgenic non-human animal. There is no guidance, nor art of record to the use of appropriate vectors, the specific promoter sequences and cloning details for all the claimed species, nor operable methods to create any transgenic animal besides the transgenic mouse.

As discussed by Peet *et al.* in the introduction, LXR receptors form heterodiameric complexes with RXR to form active complexes for the regulation of gene expression through the activation by both retinoids and oxysterols (page 693; bridging paragraph). Further, as reviewed in Evans, steroid receptors are part of a large superfamily of receptors which are activated by the binding of a steroid or in some case xenobiotic agents wherein the binding results in binding of promoter elements and activation of gene transcription (page 891; figure 2). The complex physiology of these molecules is reviewed by Beato *et al.* who conclude that 'recent developments shows that the controls of gene expression by steroid hormones is far more complex than was apparent at the time when the genes for SHRs were isolated. With more and more players getting on stage, we realize not only this complexity but also the persuasive role steroid hormones play in a vast number of physiological and pathological precesses' (pages 855-6; bridging paragraph). Manglelsdorf *et al.* described the nuclear superfamily as over 150 different proteins with a complex array of extracellular signals and transcriptional responses (page 841; first paragraph). While the review means to stress the commonalities among various signaling pathways and that 'it is possible to consider each receptor or each hormone in isolation and to extract common themes, body physiology is rarely so simple' (page 847; bottom of column 2) and concludes that while 'the advances of the last 10 years can be viewed with satisfaction, there is still a long and challenging journey ahead' (page 484; final line). Essentially, at the time of filing of the present application, LXRs represented a growing number of superfamily members with increasingly more complex function, particularly when extended to *in vivo* physiology. The

present application has defined a novel function for the LXRα *in vivo* using transgenic mice with a disrupted allele, however, the specification of the present application, nor the art of record, has resolved the many complexities of the role of this receptor in all animals, nor has it resolved the role of this molecule for use in full the scope recited in the claims.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by Mullins *et al.* who report on transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another" (page S39, Summary). Wall *et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, first paragraph). Since the applicants have not disclosed all the nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene.

Presently, to produce an animal in which the desired gene has been disrupted, embryonic stem (ES) cells are necessary. Currently, only ES cells for the mouse are available (reviewed in

Seamark and Moreadith *et al.*). Further, if methodology were available for the creation of other knock-out animals, it is not clear that such animals could be created because of the importance and complexity of LXR/RXRs in development and the normal physiology of the animal (reviewed in Beato *et al.* and Evans). Transgenic animals other than the mouse recited in claim 3 are prophetic, besides the technical limitations of creating any non-human animal which has a desired gene disrupted, the complexities identified for the creation of the transgenic animal apply to the creation of a transgenic animal which does not express a steroid/xenobiotic receptor. The lack of examples and specific guidance in the present application do not serve as a nexus between the complex role of RXR and the ability to express as transgenes or knock-out these molecules in all animals. Applicants have described a prophetic transgenic animal wherein any animal would be used to express a disrupted receptor polypeptide encompassing the recited embodiments of the claim. While the methodology to create transgenic mice is routine, the creation of any transgenic animal is not. In particular, no ES cell for animals other than mice exists to date, so the creation of animals which depend on homologous recombination are not enabled in the art. Further, while methods for the introduction of a gene are routine, the expression of the gene and resulting phenotype of the animal is not. Without an actual reduction to practice, it is possible to predict that introduction of a transgene or an alteration to a gene would result a predictable phenotype or even in a viable animal.

Method claims using the claimed non-human transgenic animal are included in this rejection because without clear guidance on how to make or use the transgenic animals

encompassed by the claims, other than the mouse, one of skill in the art would not know how to practice the claimed methods. In particular, due to the unpredictability of transgene behavior and resulting animal phenotype, one of skill in the art would not know what cholesterol-related or bile acid-related phenotypes to monitor. Further, due to the unpredictability of transgene behavior, it is not clear that other transgenic animals having a disrupted LXRα allele would have any phenotype, and the specification is silent with respect to how to use transgenic animals without a phenotype which affects cholesterol or bile acid related metabolism.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would have required undue experimentation by one of skill to practice the invention as claimed.

Written Description

Claims 1-14, 21-29, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117.

The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The specification and the art provides adequate written description for a transgenic mouse whose genome comprises a disruption of the endogenous nuclear oxysterol receptor gene (LXRα), wherein said disruption in said mouse results in the decrease of the LXRα protein and said mouse exhibits the inability to respond normally to dietary cholesterol, however the specification fails to describe the other species within the genus of any non-human animal encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of any non-human animal containing a disruption in the LXRα allele, lack a written description. The specification fails to describe molecular or morphological phenotypes which would be associated with the disruption of the LXRα allele in animals other than the mouse. The skilled artisan cannot envision all the possible phenotypes which may occur due to the disruption of the endogenous allele in species

other than the mouse, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a transgenic mouse whose genome comprises a disruption of the endogenous nuclear oxysterol receptor gene (LXRα), wherein said disruption in said mouse results in the decrease of the LXRα protein and said mouse exhibits the inability to respond normally to dietary cholesterol meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 21-29, 44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1, 2, 21, 27, 44 and 45 are unclear in the recitation of 'comprise at least one non-functional endogenous LXRα allele' or 'comprise two non-functional endogenous LXRα alleles' because it is not clear if the a transgene is introduced as a nonfunctional allele or that the endogenous allele is disrupted. Further, the metes and bounds of what is meant by 'non-functional' are not clearly defined. As described in the specification and the art of record LXR*α* has several domains and functions (DNA binding, heterodiamerization, activation domain,...) associated with these domains, and it is unclear exactly what would constitute a non-functional LXRα.

Claims 6 and 7 are unclear in the recitation of a 'nonsense mutation that truncates the LXRα products' because there is no antecedent basis for the products and it is unclear if these are transcription, translation, or some other intermediate product produced by the gene.

Claims 10 and 11 are vague and unclear in the recitation of 'contains an alteration in the regulatory region' because there is no functional language which defines what is meant by an alteration. Further, it is unclear what is meant by the regulatory region, and as such, the metes and bounds of the possible changes are not clearly defined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-9, 14, 21-29, 44 and 45 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Peet *et al.* (Cell 93:693-704; C45 in IDS).

Claims 1-9 and 14 encompass a non-human transgenic mammal and claims 44 and 45 encompass a cell comprising at least one non-functional endogenous LXRα allele. Claims 21-29 encompass methods of screening a candidate substance for the ability to reduce cholesterol (claims 21-26) and the ability to increase bile acid synthesis (claims 27-29) with said transgenic animal. Peet *et al.* teach a transgenic mouse wherein the endogenous LXRα has been disrupted through homologous recombination. The recombination results in a truncated gene through the removal of exons 3-6 (page 694; figure 1). The mice containing a homozygous disruption demonstrate no detectable levels of LXRα, while the heterozygous mice demonstrate intermediate levels relative to wild-type mice (page 694; figure 1B). The homozygous and heterozygous disruptions result in phenotypes of hepatic cholesterol which reflect the amount of expression of the disrupted LXRa (page 697; figure 3E). Finally, in view of the phenotypes of the transgenic mice and various resulting gene expression profiles, Peet *et al.* propose that these mice would be

useful as a model in screening LXRα as a pharmaceutical target (page 701; conclusion). Thus, Peet *et al.* anticipate the claims.

Conclusion

No claim is allowed. Claims 10-13 appear to be free of the prior art of record because the prior art of record fails to teach or suggest the disruption of the promoter region of the LXRα gene with an inducible/repressible promoter. However, these claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

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